

Applicants: Robert J. Winchester, et al.  
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**Amendments to the Specification:**

Please amend the paragraph appearing on page 5, lines 7-11 as follows:

**Fig 2.** Comparison of the amino acid sequence of human semaphorin III (SEQ ID NO:5), IV (SEQ ID NO:3), V (SEQ ID NO:4) and mouse semaphorin E (SEQ ID NO:1) with the predicted sequence of human semaphorin VI (SEQ ID NO:2). Nucleotide sequence of the cDNA fragment of human semaphorin VI was translated into an amino acid sequence, and compared to that of the corresponding region of human semaphorin III, IV, V and mouse semaphorin E. Conserved amino acids are indicated with boxes. One amino acid gap introduced in the human semaphorin III and V to obtain the best alignment was marked by X.

Please amend the paragraph appearing on page 5, lines 21-30 as follows:

**Fig 3.** Comparison of amino acid sequence of the human N-acetylglucosamine-6-sulfatase (SEQ ID NO:8) and predicted amino acid sequence from the *C. elegans* cosmid K09C4 (SEQ ID NO:6) and the clone ts99 (SEQ ID NO:7). Nucleotide sequence of the cDNA fragment of the clone ts99 was translated to an amino acid sequence, and the corresponding region of the human N-acetylglucosamine-6-sulfatase and *C. elegans* cosmid K09C4 were compared. Conserved amino acids are marked with boxes.

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Please amend the paragraph appearing on page 10, line 27 through page 11, line 37 as follows:

**Construction of the subtraction library and preliminary sequencing.** PolyA<sup>+</sup> RNA was isolated from the fifth passage synoviocytes using a mRNA Isolation Kit (Stratagene). 2ug of twice purified polyA<sup>+</sup> RNA was used as a template for cDNA synthesis in the RiboClone cDNA Synthesis System (Promega). The synthesized cDNA was ligated with the oligonucleotides GATCCGCGGCCGC (SEQ ID NO:9) and GCGGCCGCGT (SEQ ID NO:10) as described (26). After selection of fragments larger than 250 nucleotides by fractionation through a Sephacryl S-400 column (Pharmacia) and phosphorylation with T4 polynucleotide kinase, the cDNA was digested with the restriction enzyme MboI. The fragments were then ligated with oligonucleotides J-Bam-24 ACCGACGTCGACTATCCATGAACG (SEQ ID NO:11) and J-Bam-12 GATCCGTTCATG (SEQ ID NO:12) and amplified as described(26). The PCR products, after fractionation through Sephacryl S-400 column, were digested with MboI and they comprised the primary amplicon. DNA from rheumatoid arthritis synoviocytes was further ligated with oligonucleotides N-Bam-24 AGGCAACTGTGCTATCCGAGGGAG (SEQ ID NO:13) and N-Bam-12 GATCCTCCCTCG (SEQ ID NO:14). The hybridization was performed as described(26) except that the ratio of tester and driver was kept 1:100 throughout. 10ug of the osteoarthritis primary amplicon were hybridized with 0.1ug of the rheumatoid arthritis primary amplicon in 5ul of 24mM EPPS, pH8.0, 1mM EDTA, 1M NaCL for 20hr at 67C. The hybridized DNA was subjected to 10 cycles of PCR with N-Bam-24 as primer, followed by digestion with mung bean nuclease. One four hundredth of the digests was further amplified for 20 cycles. After digestion with MboI, the

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DNA product was ligated with oligonucleotides R-Bam-24 AGCACTCTCCAGCCTCTCACCGAG (SEQ ID NO:15) and R-Bam-12-GATCCTCGGTGA (SEQ ID NO:16). Hybridization and amplification steps were repeated. After redigestion with MboI, the resulting differentially subtracted cDNA fragments were cloned into a BamHI site of the plasmid Puc18. The recombinants were inoculated in an ordered grid pattern on nitrocellulose filters, which were then probed with the osteoarthritis cDNA amplicon <sup>32</sup>P-labeled with the Megaprime DNA labeling System (Amersham). The DNA sequence of the non-hybridized recombinants was determined in an Applied Biosystems DNA Sequencer Model 373A or 377 using standard dye terminator chemistry. The seqman module of the Lasergene program (DNASTar) was used for identification of homologous recombinants and grouping them into groups. The Genman module of the Lasergene program was used to search the GenBank databases including the expressed sequence tag database on CDROM. BLAST was used to verify the identification of sequences that showed no homology with entries in the CDROM database.

Please amend the paragraph appearing on page 14, lines 26-33 as follows:

Another clone was found to have 90% homology with mouse semaphorin E (SEQ ID NO:1) at the nucleotide level and 94% at the putative amino acid level. This suggested that the isolated clone was a human homologue of the mouse semaphorin E, and it was tentatively named human "semaphorin VI" (SEQ ID NO:2). A comparison of the amino acid sequences with the previously described human semaphorins III (SEQ ID NO:5), IV (SEQ ID NO:3), V (SEQ ID NO:4) and mouse semaphorin E is shown in Fig. 2.

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Please amend the paragraph appearing on page 14, line 35 through page 15, line 5 as follows:

Analysis of another clone showed some homology at the nucleotide level and more significantly at the putative amino acid sequence level with a variety of sulfatases. Among human genes the greatest similarity was with the human N-acetyl-glycosamine sulfatase (SEQ ID NO:8). However the sequence of this clone was most homologous with the putative amino acid sequence derived from the *C. elegans* cosmid KO9C (SEQ ID NO:7) (Fig 3).